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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,084	VAUTHIER ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *7,11-14,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-10,15,16 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5)☐ Notice of Informal Patent Application
6)☐ Other: _____.

Detailed Action

Amendments

In the reply filed April 16, 2007, Applicant has withdrawn, but amended, Claims 7 and 11-13, amended Claims 1-6 and 10, and added new claims, Claims 14-19.

Claims 7, 11-14 and 17-18 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-6, 8-10, 15-16 and 19 are under consideration.

Response to Amendment

As per Applicant's representative's request, the Examiner does not find any objection to the drawing filed on December 5, 2005, which is an English translation of the French figure legend of the drawing filed on April 28, 2005.

Priority

Acknowledgement is made of the certified translation, filed on April 17, 2007, of the French patent FR 02/11518 filed on September 17, 2002.

Accordingly, the effective priority date of the instant application is granted as September 17, 2002.

Information Disclosure Statement

Applicant has filed an Information Disclosure Statement on April 17, 2007, which has been considered. The signed and initialed PTO Form 1449 is mailed with this action.

Claim Rejections - 35 USC § 102

1. **The prior rejection of Claims 1-6 and 8-10 under 35 U.S.C. 102(a) is withdrawn** because the declaration under 37 CFR 1.132 filed April 16, 2007 is sufficient to overcome the rejection of Claims 1-6, 8-10 and 15 based upon the establishment that the publication of Bourdon and Debuire (* of record in IDS) is not by an inventive entity other than Applicant.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

2. **Claims 1-6 and 8-10 stand, and Claims 15-16 and 19 are newly rejected under 35 U.S.C. 103(a)** as being obvious over Chauvierre et al, WO 02/39979 A1) and Desai et al (U. S. Patent No. 6,096,331).

The prior stated rejection has been modified slightly to reflect the amendments to the instant claim limitations.

Chauvierre et al teach the synthesis of nanoparticles of 1nm to 1mm (pg 7, line 30; pg 9, line 5) comprising a block copolymer comprising at least one segment having the formula as taught in Formula I (pg 3, lines 12-28), wherein "X" may be a "CN" moiety, wherein the hydrophobic segment may be a poly(alkylcyanoacrylate) (pg 8, line 29-pg 9, line 3) conjugated to a hydrophilic saccharide that may be heparin (pg 5, line 29; pg 9, line 1). Chauvierre et al teach that the inventive delivery system(s) may be used to administer a therapeutic agent to an animal or patient (pg 1, line 15; pg 9, lines 22-24).

Chauvierre et al do not teach the use of the heparin-coated poly(cyanoacrylate) nanoparticle for the delivery of hemoproteins such as hemoglobin. However, at the time of the invention, Desai et al taught the synthesis of nanoparticles comprising synthetic block copolymers (column 10, lines 3-22), attached to biocompatible materials, i.e. polysaccharides (column 9, lines 42-49). Desai et al do not explicitly disclose heparin as a contemplated polysaccharide; however, absent evidence to the contrary, the art recognizes that heparin is a polysaccharide. Desai et al also contemplate that hemoglobin would be present in the polymeric shell (column 9, line 54; column 11, line 63), thereby providing a blood substitute.

Neither Chauvierre et al nor Desai et al disclose the hemoglobin composition to be "gas-associated". However, the instant claims do not recite the minimum amount of gas necessary to be associated with the composition. Absent evidence to the contrary, the hemoglobin composition will inherently possess at least one gas molecule, as there is no evidence to demonstrate that the composition is "gas-free". Furthermore, given that Desai et al contemplate the use of a hemoglobin-containing nanoparticle for use as a blood substitute, one of ordinary skill in the art would reasonably expect said composition to be "gas-associated".

It would have been obvious to one of ordinary skill in the art to modify the nanoparticle of Chauvierre et al to include a hemoprotein such as hemoglobin as taught by Desai et al with a reasonable chance of success because Desai et al teach that the biocompatible agent, that is, hemoglobin may be associated with the nanoparticle shell comprising a polysaccharide so as to be useful as a blood substitute, and the art that has long recognized that heparin, being polyanionic in nature, has a high affinity for basic proteins like hemoglobin (Haney et al, 2000; reference 19 of Chauvierre et al, 2004a* of record). An artisan would have been motivated to add hemoglobin to the nanoparticle of Chauvierre et al because the heparin moiety, well known in the art to act as an anti-coagulant as well as to inhibit complement activation, already tailors the nanoparticle for increased circulating half-life of the nanoparticle, and thus would provide an artisan with the desired delivery vehicle for a blood substitute.

Thus, the invention as a whole is *prima facie* obvious.

Applicant's Arguments

Applicant argues that:

a) the nanoparticles of Desai et al are distinctly different from the nanoparticles of the instant application because the biological agent is "encapsulated", wherein the shell forming the capsule is polymeric in nature.

b) Applicant argues that Desai does not contemplate particles whose core comprises a hydrophobic polymeric segment covalently linked to one or both ends of an oligosaccharide or polysaccharide hydrophilic segment that lies at the surface of the particle, much less a hemoprotein associated with an oligosaccharide or polysaccharide segment coating these particles.

c) Desai et al does not contemplate, teach or suggest sequenced block copolymers comprising an oligosaccharide or polysaccharide hydrophilic segment covalently attached via at least one end of its ends to at least one hydrophobic polymer in a sequenced fashion.

d) Desai et al does not teach or suggest hemoglobin associated with a particle shell comprising a polysaccharide or polymeric nanoparticle.

e) The microcapsules of Desai lack the primary attribute necessary for use as a blood substitute or depolluting agent; namely, a long circulating half-life in the blood stream. Desai's microcapsules are designed to localize in certain tissues after administration. See, for example, column 6 lines 46-56 and paragraph bridging columns 6 and 7. Clearly, the object of Desai's teachings is to provide microcapsules that accumulate in certain tissues for localized therapeutic applications (See column 8 lines 61-64). In contrast, the block copolymer particles described in

Chauvierre are designed to prevent their uptake by the organism's nonspecific immune defense system, and as a result, to increase their circulation in the blood stream. In contrast to Desai's microcapsules, the particles of Chauvierre are designed to avoid accumulation in organs of the mononuclear phagocyte system, including the liver and the spleen.

f) the cited combined references provide no reasonable expectation of success.

g) There is no evidence or suggestion in Chauvierre or Desai, or in the general knowledge in the art at the time the invention was made, that hemoglobin, or hemoproteins in general, may associate with oligo- or polysaccharide-coated particles, while preserving its ability to reversibly bind ligands (e.g., oxygen, carbon monoxide or nitric oxide gases).

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a-e), in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the instant case, Chauvierre et al (WO 02/39979 A1) disclose sequenced block copolymers, wherein the hydrophobic segment is of the Formula I, wherein the saccharide is bound by either one of its ends to a single hydrophobic segment having Formula I, or by each one of its two ends bound to a hydrophobic segment having Formula I, the two hydrophobic segments being identical or different, wherein the oligosaccharide or polysaccharide may be dextran, sulfated dextran or heparin, wherein the hydrophobic segments form groups that constitute the core and the segments of saccharide nature are arranged in a brush crown all around the core, wherein the particles have a size between 1nm and 1mm, preferably between 60nm and 100μm, and wherein particles having a size between 1 and 1000nm are called nanoparticles. These particles may exhibit a biological activity because they may incorporate in addition a biologically or pharmaceutically active ingredient, e.g. proteins.

Chauvierre et al do not explicitly disclose the incorporation of hemoglobin into the nanoparticle. However, at the time of the invention, Desai et al (U. S. Patent No. 6,096,331) specifically contemplate hemoglobin be delivered as part of a polymeric shell of a nanoparticle (col. 6, line 21), specifically disclosing the use of polysaccharides, e.g. dextran, and the protein

hemoglobin, wherein such biocompatible materials are crosslinked or covalently bonded (col. 9, lines 41-55; col. 10, lines 12-13; col. 11, lines 19-21), thereby providing a blood substitute having a high binding capacity for oxygen (col. 11, lines 64-67). Thus, the hemoglobin is not "encapsulated" as Applicant argues.

Neither Chauvierre et al nor Desai et al disclose the hemoglobin composition to be "gas-associated". However, as discussed above, the instant claims do not recite the minimum amount of gas necessary to be associated with the composition. Absent evidence to the contrary, the hemoglobin composition will inherently possess at least one gas molecule, as there is no evidence to demonstrate that the composition is "gas-free". Furthermore, given that Desai et al contemplate the use of a hemoglobin-containing nanoparticle for use as a blood substitute, one of ordinary skill in the art would reasonably expect said composition to be "gas-associated".

The combined references teach the instantly claimed nanoparticle composition whose core comprises the hydrophobic segment of Formula I, wherein the oligosaccharide or polysaccharide segment, specifically heparin, dextran or dextran sulfate, lies at the surface of the particle, and wherein a hemoprotein, specifically a normal hemoprotein such as hemoglobin, ia associated with the oligosaccharide or polysaccharide segment.

With respect to f), it is unclear how an ordinary artisan would not have a reasonable expectation of success when the prior art teaches how to make a nanoparticle comprising the essential features of the composition. The artisan need only follow the teachings of Desai et al to add hemoglobin to the nanoparticle of Chauvierre et al to create the instantly claimed composition, the reasonable expectation of success coming from the art that has long recognized that heparin, being polyanionic in nature, has a high affinity for basic proteins like hemoglobin (Haney et al, 2000; reference 19 of Chauvierre et al, 2004a* of record), for example.

With respect to g), in response to Applicant's argument that the references fail to show certain features of Applicant's invention, it is noted that the features upon which Applicant relies (i.e., that hemoglobin, or hemoproteins in general, may associate with oligo- or polysaccharide-coated particles, while preserving its ability to reversibly bind ligands (e.g., oxygen, carbon monoxide or nitric oxide gases) are not recited in the rejected claim(s). Although the claims are

interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, the Office does not have laboratory facilities to demonstrate whether or not a nanoparticle composition comprising the core and shell structure comprising heparin as taught by Chauvierre et al, said particle further comprising hemoglobin as taught by Desai et al would, or would not possess the instantly argued inventive features. Thus, the burden is shifted to Applicant to demonstrate that such a composition would not have such elements.

Conclusion

3. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Q. JANICE LI, M.D.
PRIMARY EXAMINER